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EXAMINER
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ART UNIT	PAPER NUMBER
1642	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/445,576	Thorgersen et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 19, 22-24, and 68-105* is/are pending in the application.

4a) Of the above, claim(s) *92, 93, 95-97, 100, 101, 104, and 105* is/are withdrawn from consideration.

5) ☒ Claim(s) *78-81* is/are allowed.

6) ☒ Claim(s) *1, 19, 22-24, 68-77, 82-91, 94, 98, 99, 102, and 103* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *12*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Acknowledgment is made of applicant's election, with traverse, of Group II drawn to oligomer peptide constructs and methods of preparing dimeric and trimeric peptide constructs. The traversal is on the grounds that the restriction is improper, as the claims directed to the oligomer of Group II are patentable and hence the method of using the oligomers in the method of Group V share the same inventive concept. This has been considered but not found persuasive. As demonstrated by Thogersen et al, Kastrup et al and Hoppe et al (cited in art rejections set forth in this office action), the oligomers of Group II lack novelty over the art, and thus claims drawn to this product and methods of making and using said product do not share a special technical feature. Thus, as Unity of Invention is lacking, the inventions are held to be distinct, and restriction for examination purposes as indicated is proper.

After examination of the application, and review and reconsideration of the restriction requirement, Group I, drawn to monomer peptide constructs, will be rejoined to Group II, drawn to oligomer peptide constructs.

Claims 2-18, 20, 21, 25-33, 35-39, 47, 48 and 51-67 have been canceled. Claims 22-24 have been amended. Claims 68-105 have been added. Claims 1, 19, 22-24 and 68-105 are pending. Claims 92, 93, 95-97, 100, 101, 104 and 105, drawn to non-elected inventions, are withdrawn from consideration. Claims 1, 19, 22-24, 68-91, 94, 98, 99, 102 and 103 are examined on the merits.

Specification

2. The disclosure is objected to because of the following informalities:

(A) Page 15, line 33, is missing words, as indicated by the two dashes.

(B) The specification lacks an abstract.

(D) The specification is objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. When the specification of a patent application discusses a sequence listing that

is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application. Applicant has amended the specification in order to incorporate sequence identifiers for recited sequences in the Figures. However, the following defects are present:

In Figure 3, line 7, a sequence identifier for has not been incorporated in the description for the peptide MGSHHHHHH, and it is unclear if SEQ ID NO:43 and 44 are the sequence identifiers for the two DNA segments on line 8.

In Figure 5, line 2 of both pT7CIIH6 and pT7H6, there is no sequence identifier for the "ATCGTGTA" fragment.

In Figure 7, , under the description for T3, it is stated that SEQ ID NO:53 encodes amino acids 10-19 of SEQ ID NO:30. However, the figure includes only amino acids 10-18 of SEQ ID NO:30.

In Figure 13, the description refers back to Figure 3 for identification. However, descriptions of all figures should be independently in sequence compliance. Further, Figure 3 can not be relied upon to identify the sequences in Figure 13 as Figure 3 does not include the fragment "AAGCTT" above the label Hind III.

In Figure 17, the description refers back to Figure 15 for identification. The description of all figures should be independently in sequence compliance. Further, Figure 15 cannot be relied upon for identification of all the sequences in Figure 17, as the second DNA fragment in the second line of the figure differs between Figures 15 and 17 ("CTGAATGGGGCCS" versus "CTGAATGGGGCCTA").

In Figure 19, again the description refers back to Figure 15, and is therefore not conforming with sequence compliance.

Appropriate correction is required.

3. The drawings are objected to because of the following defects:

(A) The description of Figure 1 on page 8, line 14, refers to residue K52 which is not present in Figure 1.

(B) The description of figure 3 indicates that Tripa and Tripb harbor the tetranectin amino acid sequence from E1 to T48 and E1 to K52, respectively. However, there is no indication of where the T48 or the K52 residues are located within the Tripa or Tripb sequences set forth in the drawings, and further, the figure does not include a K residue in the Tripb sequence.

(C) The description of Figure 5 discusses SEQ ID NO:11 and 12, but it is unclear where these sequences are located within the figure. The description further indicates that the dashes joining SEQ ID NO:46 to SEQ ID NO:47 represent "unquoted DNA". However, the Figure designates that area as "CII", and it is not clear what significance can be attributed to CII.

(D) The description of Figures 3 and 7 both refer to SEQ ID NO:7, but it is not clear where SEQ ID NO:7 is located within each Figure.

(D) The description of Figure 17 discusses SEQ ID NO:20, but it is unclear where this sequence is located within the figure.

A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

4. The amendments filed March 1, 2002 and February 2, 2001 are objected to under 35 U.S.C. 132 because they introduce new matter into the disclosure. 35 U.S.C. 132 states that no

amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendments to the specification filed February 2, 2001:

Page 2, line 20 to line 2 of page 3, which states "SEQ ID NO:40 and 41 are portions of a larger Tripa DNA sequence". There is no support in the specification or Figure 3 for Tripa to be larger than Tripa as indicated in Figure 3.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

5. Claim 101 is objected to because of the following informalities: The word "of" is misspelled as "og" and "the buccal" is recited twice. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 22-24, 76, 82, 84, 87-90 and 94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22 and 23 are rendered vague and indefinite in the recitation of "the at least one heterologous moiety which is positioned N-terminally to a TTSE, and the at least one heterologous moiety which is positioned C-terminally to a TTSE" which lacks proper antecedent basis in claim 68 which does not refer to the position of the heterologous moiety. Amendment of the claims to recite ---the at least one heterologous moiety is positioned N-terminally to a TSE,

and the at least one heterologous moiety w is positioned C-terminally to a TTSE--- would abrogate this rejection.

Claim 24 recites "a trimeric polypeptide complex wherein each monomer polypeptide construct.... is designed so as to disfavor formation of trimers including two monomer polypeptide constructs having identical TTSEs". It is unclear if the trimeric polypeptide complex includes two monomer peptide constructs having identical TTSEs or the trimers that are to be disfavored include two monomer polypeptide constructs having identical TTSEs. Further, it is unclear in the relationship between a trimeric polypeptide complex and the with designing of monomer polypeptide constructs which disfavor the formation of trimers. Claim 24 also fails to defining precisely how the monomer peptide constructs were designed in order to disfavor the formation of trimers. A suggested amendment to the claim would read, --- a trimeric polypeptide complex comprising a monomer construct containing two TTSEs linked together by a spacer group, and a monomer construct containing a single TTSE, said monomer construct containing two TTSEs preferentially complexing with said monomer construct containing a single TTSE.---

Claim 76 recites "the amino acid residues of C50 to K52 (exon 3)" and is vague and indefinite as the specification of a short amino acid sequence of three residues (C50 to K52) conflicts with the longer amino acid sequence encoded by exon 3, and it is unclear if applicant intends to claim three amino acids of exon 3, or exon 3 in its entirety. For purpose of examination, the claim will be read as "the amino acid residues of C50 to K52 in exon 3".

Claim 82 recites "trimeric polypeptide complex...which is stable in the temperature range 50-70 [degrees C]". The claim is vague and indefinite as it lacks a qualifying statement for how such stability is to be measured or the physical characteristics associated with the claimed stable trimeric polypeptide complex.. As the trimeric polypeptide complex of claim 68 contains at least one heterologous moiety in addition to the three TTSE monomer polypeptides, it is not clear if "stable" refers to the ability of the TTSE to exist as a trimer, or if "stable"refers to retaining a

functional activity associated with the heterologous moiety or both. For purpose of examination all possibilities will be considered.

Claim 84 recites "heterologous moiety is....a group facilitating conjugation of the polypeptide to a target". It is unclear if "the polypeptide" refers to the trimeric polypeptide complex or the heterologous moiety. The nature of "conjugation" is also unclear with respect to the formation of a covalent or non-covalent bonds. For purpose of examination, the claim will be read as ---heterologous moiety is....a group facilitating conjugation of said trimeric polypeptide complex to a target, wherein conjugation encompasses both covalent and non-covalent linkages--.

Claim 84 recites "a non-proteinaceous polymer such as a polymeric alkaloid". The phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 84 recites an improper Markush group by the incorporation of the phrase "a lipid and a polyamine;". The applicant is referred to MPEP § 2173.05(h) and advised to reformat the claim to read "wherein R is a material selected from the group consisting of A, B, C and D," or "wherein R is A, B, C, or D."

Claim 87 recites "the trimeric polypeptide complex...which comprises at least one heterologous moiety which is positioned N-terminally to the monomer polypeptide, and at least one heterologous moiety which is positioned C-terminally to the monomer polypeptide". The meets and bounds of the claim cannot be determined as the claim fails to specify if the heterologous moiety which is positioned N-terminally and C-terminally to the monomer polypeptide are on the same or separate monomer polypeptides, as the trimeric complex consists of three monomer polypeptides.

Claim 88 recites "via a peptide bond to the - or C-terminus of the monomer peptide chain", and thus is missing a designation before the first dash (-). For purpose of examination the claim will be read as ---via a peptide bond to the N- or C- terminus of the monomer peptide chain".

The recitation of the phrase "and optionally subjecting the polypeptide complex to further processing" in claim 90 renders the claim indefinite because it is unclear whether the limitation of subjecting the polypeptide complex to further processing is part of the claimed invention. See MPEP § 2173.05(d). For purpose of examination the cited phrase will not be considered an embodiment of claim 90.

Claim 94 recites, "said product having low antigenicity in humans relative to formulations comprising one or more components of non-human origin". The term "low" is a relative term, defined by comparison to the antigenicity of formulations "comprising one or more components of non-human origin". As the number of formulations comprising components of non-human origin are legion, one cannot reasonably asses the difference in antigenicity of the claimed trimeric polypeptide complexes comprising at least one heterologous moiety versus formulations comprising the genus of "components of non-human origin". Further, the specification does not provide a standard for ascertaining the requisite degree that constitutes "low", and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. .

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 19, 68-77, 83, 86, 88, 90 and 98 are rejected under 35 U.S.C. 102(b) as being anticipated by Thogersen et al (WO 94/18227, reference AA of the IDS filed April 23, 2001) as evidenced by Kastrup et al (Acta Cryst, January 1997, Vol. D53, pp. 108-111, reference AX of

the IDS filed April 23, 2001) and as evidenced by the abstract of Nielsen et al (FEBS Lett 1997, vol. 412, pp. 388-396, reference BC of the IDS filed April 23, 2001). Claim 1 is drawn to a monomer peptide construct comprising at least one tetranectin trimerizing structural element (TTSE), which is linked to a heterologous moiety, said TTSE capable of forming a stable triple alpha helical coiled-coil complex with two other TTSE. Claim 1 (and page 7, lines 6-17 of the instant specification) further excludes fusion proteins taught in the prior art, said fusion proteins made to facilitate expression and/or purification of said monomer peptide construct. The specification defines the tetranectin trimerizing structural element as the consensus sequence indicated in figure 2. Dependent claim 19 is drawn to an oligomer comprising at least two monomer peptide constructs according to claim 1. The specification defines oligomer on page 19, lines 6-10, as being a non-covalent complex of two or more monomer peptide constructs.

Claim 19 is drawn to a trimeric polypeptide complex comprising three monomer peptides wherein each of said monomer polypeptides comprises a TTSE, said TTSE being a polypeptide having at least 68% sequence identity with the consensus sequence shown in Figure 2, and at least one of said monomer polypeptides is covalently linked to a heterologous moiety. Dependent claims 69-72 are drawn to the sequence identity with the consensus sequence being 75%, 81%, 87% and 92%, respectively.

Claim 73 specifically embodies the TTSE as the consensus sequence shown in figure 2. Claim 74 specifically embodies a TTSE derived from human tetranectin, murine tetranectin, bovine cartilage C-type lectin, or shark cartilage C-type lectin.

Claim 75 is drawn to the trimeric polypeptide complexes of claim 74, wherein the TTSE is derived from human tetranectin and comprises the resides V17 to V49 (exon 2). Claim 76 is dependent upon claim 75, wherein the TTSE derived from human tetranectin further comprises the amino acid residues of C50 to K52 of exon 3. Claim 77 is drawn to the trimeric complex of claim 68, wherein the monomer polypeptides further comprise the amino acid residues E1 to D16 (exon 1).

Claim 83 specifically embodies the trimeric polypeptide complex of claim 68 comprising 2 to 6 heterologous moieties. Claim 86 is drawn to the trimeric polypeptide complex of claim 68 wherein said at least one heterology moiety is positioned N-terminally to the monomer polypeptide. Claim 88 is drawn to the linkage of the at least one heterologous moiety to the monomer peptide via a peptide bond to the N-terminus or C-terminus of the monomer peptide, via a peptide bond to a side chain in the monomer peptide, via a peptide bond to a cysteine residue or a combination of these locations.

Claim 90 is drawn to a method of preparing a trimeric polypeptide complex which comprises admixing three monomer polypeptides having at least one heterologous moiety, effecting complex formation between said monomer peptides, and isolating the resulting trimeric polypeptide complex.

Claim 98 is drawn to a composition comprising the trimeric polypeptide complex of claim 68.

Thogersen et al disclose the sequence for human tetranectin comprising the consensus sequence of Figure 2 and comprising residues E1 to K52, and a peptide construct pT7H6FX-TETN (page 91, lines 20-21) expressing the tetranectin monomer linked via a peptide bond at the N-terminus (page 91, lines 10 to 18 indicate fusion of the SEQ ID N:37 to the tetranectin Glu1 residue) to heterologous sequence encoding a cleavage site for the bovine restriction protease. The inclusion of the heterologous sequence encoding the cleavage site for said protease was to verify the activity of the monomer peptide construct after a refolding procedure (page 92, line 25 to page 93, line 17), and thus does not constitute heterologous sequence added to the tetranectin monomer in order to facilitate expression and/or purification. Thogersen et al disclose that said tetranectin monomer converted to the correctly folded tetranectin tetramer in the presence of CaCl2. (Page 93, lines 29-33). Thogersen et al disclose the isolation of recombinant tetranectin by ion-exchange chromatography, said recombinant tetranectin behaving identically to naturally

isolated human tetranectin, believed to be a tetramer. Thogersen et al disclose a composition comprising the oligomerized tetranectin (page 93, lines 6-9).

Kastrup et al disclose that although the prior art taught that tetranectin occurred as a tetramer in solution, X-ray analysis and studies with recombinant tetranectin as well as human tetranectin from plasma indicate that tetranectin is a trimer in the crystal and solution state (last sentence of the abstract and page 111, last paragraph). Thus Kastrup et al provides evidence that tetranectin folds into a trimer, not a tetramer as taught by the prior art. Kastrup et al disclose that the amino acids encoded by exons 1 and 2 of human tetranectin stabilize the trimerization of tetranectin in solution and in the crystal state (page 111, last paragraph).

The ability of the monomer peptide construct disclosed by Thogersen et al to form a stable triple alpha helical coiled-coil complex with two other TTSE is inherent in the structure of tetranectin, as evidenced by the abstract of Nielsen et al.

Therefore, Thogersen et al discloses a monomer peptide constructs of tetranectin fused to a heterologous sequence coding for a protein not to be used to facilitate purification or expression of the tetranectin, said monomer construct forming an oligomer upon exposure to CaCl2. Thogersen et al disclose a method for preparing trimeric polypeptide complexes comprising admixing of monomer polypeptide constructs, followed by the formation of oligomerized tetranectin in the presence of CaCl2 as this procedure yielded tetranectin which was identical to tetranectin isolated from human beings. Thogersen et al thus discloses the specific embodiments of claim 90. Thogersen et al incorrectly states that the oligomer formed is a tetramer on the basis of prior art teachings. Kastrup et al discloses that the prior art teachings regarding the tetrameric nature of the tetranectin oligomer are incorrect, and that the tetranectin oligomer is a trimer. Thus, it can be concluded that the oligomer construct of Thogersen et al is a trimer, said trimer comprising 3 heterologous moieties, as each tetranectin molecule in the trimer is fused to the heterologous protein. The trimeric oligomer construct exists as a triple alpha helical coiled-coil complex. This physical state is an inherent property of the tetranectin trimer.

As the human tetranectin sequence disclosed by Thogersen et al comprises a covalently linked heterologous moiety of the bovine serum protease, the amino acid residues of exons 1 through 3 of human tetranectin which have 100% sequence identity to the consensus sequence of Fig 2, the specific embodiments of claims 68-77 have been met.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 22, 23, 68-77, 82-90, 94, 98, 99, 102 and 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thogersen et al (WO 94/18227, reference AA of the IDS filed April 23, 2001), Kastrup et al (Acta Cryst, January 1997, Vol. D53, pp. 108-111, reference AX of the IDS filed April 23, 2001), in view of Hoppe et al (WO 95/31540, reference AB of the IDS filed April 23, 2001).

The specific embodiments of claims 68-77, 83, 86, 88, 90 and 98 and the teachings of Thogersen et al, Kastrup et al are set forth in the rejection under 35 U.S.C. 102(b), above.

Claim 22 is drawn to the trimeric polypeptide complex of claim 68, wherein the at least one heterologous moiety is positioned N-terminally to the TSE and the at least one heterologous moiety is positioned C-terminally to the TTSE are on the same monomer polypeptide. Claim 23 is drawn to the trimeric polypeptide complex of claim 68, wherein the at least one heterologous moiety is positioned N-terminally to the TSE and the at least one heterologous moiety is positioned C-terminally to the TTSE are on the separate monomer polypeptides.

Claim 82 is drawn to the trimeric polypeptide complexes of claim 68 which are stable in the temperature range of 50-70.

Claim 84 is drawn to the trimeric polypeptide complex of claim 68 wherein at least one heterologous moiety is selected from the group consisting of a ligand binding structure; a toxin; a detectable label; an in situ activatable substance; an enzyme; a radioactive moiety; a cytokine; a polymeric alkaloid, a polyalcohol, a polysaccharide, a lipid, a polyamine, a photo cross-linking agent, and a group facilitating the conjugation of said polypeptide complex to a target.

Claim 85 is drawn to the trimeric polypeptide complex of claim 68 wherein said at least one heterology moiety is positioned C-terminally. Claim 87 embodies the trimeric polypeptide complex of claim 68, wherein the at least one heterologous polypeptide is positioned C-terminally and N-terminally to the monomer peptide. Claim 89 embodies claim 68, wherein the trimeric polypeptide complex lacks any free amino and/ or carboxyl groups on the heterologous moiety.

Claim 94 is drawn to a chimeric product comprising a trimeric polypeptide complex according to claim 98, said product having low antigenicity in humans relative to formulations comprising one or more components of non-human origin.

Claim 99 is drawn to the composition of claim 98 wherein the trimeric polypeptide complex is comprised in a liposome.

Claim 102 is drawn to a diagnostic agent comprising the trimeric polypeptide complex according to claim 68. Claim 103, dependent upon claim 102 is drawn to the at least one heterologous moiety is a detectable label.

Thogersen et al, as evidenced by Kastrup et al, teach that tetranectin forms trimers in solution and in the crystal state. Thogersen et al teach that the oligomerization of the tetranectin monomer is not interrupted by a heterologous moiety fused N-terminally to the tetranectin polypeptide. Kastrup et al teach that the structural feature of tetranectin responsible for trimerization is in the polypeptide encoded by exons 1 and 2 of the tetranectin gene (page 111, last sentence). Kastrup et al compares full length tetranectin with mannose binding protein which also has trimerizing ability. Kastrup et al points out that the neck region of mannose binding protein has been shown to be responsible for stabilization of the conformation of the C-terminal part of the trimer. Thogersen et al do not teach:

a trimeric polypeptide complex in which a heterologous moiety is position C-terminally to the TTSE, either on the same or different monomer polypeptide;

the trimeric polypeptide complex comprising at least one heterologous moiety, wherein the heterologous moiety is selected from the group consisting of a ligand binding structure, a detectable label, and in situ activatable substance, and enzyme, a cytokine, a polymeric alkaloid, a polyalcohol, a polysaccharide, a lipid, a photo cross-linking agent and a group facilitating conjugation of the polypeptide to a target;

a trimeric polypeptide complex lacking free amino and/or carboxyl groups in the heterologous moiety;

a chimeric product comprising a trimeric polypeptide complex, said product having low antigenicity in human relative to formulations comprising one or more components of non-human origin;

a diagnostic agent comprising the trimeric polypeptide complex of claim 68, wherein the at least one heterologous moiety is a detectable label.

Hoppe et al teach:

trimerizing polypeptides comprising heterologous moieties attached N-terminally or C-terminally or both N and C terminally to a collectin-neck region polypeptide, said neck-region polypeptide able to form a trimer and the trimeric polypeptide complex comprising at least 2, 3, 4, 5 or 6 heterologous moieties (page 3, lines 9-18);

the trimeric polypeptide complex comprising at least one heterologous moiety selected from the group consisting of a ligand binding structure (page 10, lines 13-16) and a cytokine (interleukins, page 20, lines 17-18 and page 19, lines 16-21), a detectable label (page 21, lines 7-9, page 22, line 1), an in situ activatable substance (for example, morphine, page 21, line 2), an enzyme (page 23, lines 19-24), a polymeric alkaloid and a polyalcohol (included by organic compounds on page 21 lines 2-3), a polysaccharide (carbohydrate page 21, lines 11-12), a lipid (page 21, lines 13-17), and a group facilitating conjugation of the trimeric polypeptide complex to a target (single chain antibody to conjugate the trimeric polypeptide complex to a solid matrix, page 23, lines 3-18) a photo cross-linking agent (page 20, lines 21-23); and a trimeric polypeptide complex incorporated into a liposome (page 21, lines 13-17)

a diagnostic agent comprising a the trimeric polypeptide complexes (page 8-12) and detectable labels (page 22, line 1)

humanized neck region polypeptides and /or heterologous sequences, to minimize the likelihood of an immune response when said neck region polypeptide and heterologous sequences are administered to an individual (page 10, lines 1-6), thus anticipating a chimeric molecule having low antigenicity relative to the non-chimeric molecule having non-human components;

the chemical modification of heterologous sequences at lysine, glutamate, histidine and tyrosine (page 4, lines 14-15), said modification including side chains of the heterologous moiety, said modifications when complete, would be expected to render the heterologous sequence without free amino or carboxyl groups, and the chemical modification of cysteine residues (page 4, lines 2-5);

a trimeric polypeptide complex which retains its ability to exist as a trimer after heating to 50 degrees (abstract).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the tetranectin monomer for the collectin neck region peptide disclosed by Hoppe et al and symbolized by the structure on page 3, lines 11-16. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of:

Kastrup et al on the ability of tetranectin to from trimers in solution (abstract),

Thogersen et al on the ability of tetranectin fused to a heterologous sequence to form oligomers in solution which are disclosed by Kastrup et al to be trimers, and

Hoppe et al on the presence of a "neck region" in mannose binding protein similar to the collectin neck region polypeptides (page 7, lines 11) and the teachings of Kastrup et al on the similarity of tetranectin to mannose binding protein, and the existence of neck region in mannose binding protein responsible for trimerization (page 111, last paragraph). As it can be inferred that tetranectin has a "neck region" responsible for trimerization similar to the disclosed collectin neck regions by acknowledged similarity to mannose binding protein, substitution of the tetranectin monomer for the collectin neck region peptide would result in a monomer having the same ability to trimerize as the collectin neck region peptide.

12. Claims 22, 23, 68-77, 82-91, 94, 102 and 103 rejected under 35 U.S.C. 103(a) as being unpatentable over Thogersen et al (WO 94/18227, reference AA of the IDS filed April 23, 2001), and Kastrup et al (Acta Cryst, January 1997, Vol. D53, pp. 108-111, reference AX of the IDS filed April 23, 2001), and the abstract of Nielsen et al (FEBS Lett 1997, vol. 412, pp. 388-396, reference BC of the IDS filed April 23, 2001) in view of Hoppe et al (WO 95/31540, reference AB of the IDS filed April 23, 2001) as applied to claims 22, 23, 68-77, 82-90, 94, 102 and 103 above, and further in view of Baker et al (US 5,627,073).

The embodiments of claims 22, 23, 68-77, 82-91, 94, 102 and 103 and teachings of Thogersen et al, Kastrup et al, and Nielsen et al and Hoppe et al are set forth in section 10, above.

Claim 91 is drawn to a kit comprising the trimeric polypeptide complex of claim 68. The combination of Thogersen et al, Kastrup et al, and Nielsen et al and Hoppe et al render obvious a trimeric polypeptide complex wherein a heterologous moiety is an antibody and an additional moiety is a detectable label, said trimeric complex being used as a diagnostic agent. Neither Thogersen et al, Kastrup et al, and Nielsen et al and Hoppe et al teach a kit comprising a trimeric polypeptide complex.

Baker et al teach an antibody which binds to cardiotrophin-1, a detectable label for said antibody and a kit comprising said antibody (claims 17 and 18).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the diagnostic agent comprising the trimeric polypeptide complex of tetranectin linked to an antibody and a detectable label as taught by the combination of Thogersen et al, Kastrup et al, and Nielsen et al and Hoppe et al for the anti-cardiotrophin-1 antibody, detectable label and kit comprising said antibody as taught by Baker et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Baker et al on the use of an antibody packaged in a kit.

13. Claims 24 and 78-81 are free of the art.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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